Articles

Ethical Considerations in Ending Exploratory Brain–Computer Interface Research Studies in Locked-in Syndrome

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Abstract: Brain–computer interface (BCI) is a promising technology for restoring communication in individuals with locked-in syndrome (LIS). BCI technology offers a potential tool for individuals with impaired or absent means of effective communication to use brain activity to control an output device such as a computer keyboard. Exploratory studies of BCI devices for communication in people with LIS are underway. Research with individuals with LIS presents not only technological challenges, but ethical challenges as well. Whereas recent attention has been focused on ethical issues that arise at the initiation of studies, such as how to obtain valid consent, relatively little attention has been given to issues at the conclusion of studies. BCI research in LIS highlights one such challenge: How to decide when an exploratory BCI research study should end. In this article, we present the case of an individual with presumed LIS enrolled in an exploratory BCI study. We consider whether two common ethical frameworks for stopping randomized clinical trials—equipoise and nonexploitation—can be usefully applied to elucidating researcher obligations to end exploratory BCI research. We argue that neither framework is a good fit for exploratory BCI research. Instead, we apply recent work on clinician-researcher fiduciary obligations and in turn offer some preliminary recommendations for BCI researchers on how to end exploratory BCI studies.

Keywords: Brain–computer interface (BCI); locked-in syndrome (LIS); exploratory research; randomized clinical trials

Introduction

Locked-in syndrome (LIS) is a condition involving loss of motor function, including the ability to speak. Diagnostic categories of LIS include individuals with *incomplete* LIS who retain some residual motor function (e.g., finger or head movement), individuals with *classic* LIS who are paralyzed but only retain the ability to communicate by blinking or moving their eyes, and individuals with *total* LIS who lack all voluntary movement.[1] LIS is often associated with amyotrophic lateral sclerosis (ALS), a neurodegenerative disease that slowly paralyzes an individual over the course of years. ALS affects approximately 20,000 individuals in the United States at any given time. Although median survival rates have been estimated between 20 and 48 months, it is worth noting that at least 10 percent of these patients live longer than 10 years.[2] This timeline is particularly troubling given the increasing communication challenges presented by illness progression. Other conditions that can lead to a locked-in state include brain stem stroke, traumatic brain injury, and other neurological insults.[3]

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BCI research is a promising approach to restoring communication access to those with total LIS. BCI technology seeks to build alternative computer input schemes, which rely on a user's brain activity. Although implanted electrodes can be used as a source of neural signals,[4] skull surface electroencephalography (EEG) is the most common noninvasive BCI signal. Classic EEG BCI responses include imagined hand or foot movement, a visual response to blinking light, or a unique response to a surprising element of a sequence (P300).[5] For example, an EEG-based BCI system could allow an individual to select a letter of the alphabet by successively dividing and discarding unwanted letters. EEG detection of users' intent to move their right hand, for example, could indicate that their target letter is in the first half of the alphabet (and that the latter half of the alphabet is unnecessary, and therefore discarded). This divide-and-discard operation could be repeated over and over to progressively home in on a user's desired letter. Several methods of typing and message selection have been proposed for BCI systems.[6]

Initiating BCI research in people with LIS raises ethical issues.[7] Some have argued that it is ethically suspect to conduct communication research with individuals who are locked in or may become locked in because of poor quality of life in LIS.[8] This view has been challenged on several grounds: (1) it presumes people with LIS do not lead meaningful lives (contrary to recent evidence[9]), (2) it denies individuals and surrogates the opportunity to participate in research,[10] (3) it undermines the exercise of autonomy,[11] and (4) it may result in a violation of basic human rights.[12] These considerations are important in that more than 80 percent of patients severely affected by ALS in a recent survey expressed interest in BCI for communication support.[13]

For those with LIS or their surrogates who express interest in BCI research, ensuring meaningful informed consent is an obstacle. Informed consent is a foundational principle for participation in research and is grounded in a commitment to respect for persons.[14] The inability to communicate a desire to participate or decline participation in a research trial—when the capacity to form and maintain that desire is otherwise intact—undermines the practice of informed consent. Individuals cannot give an informed consent for research if their autonomous choices cannot be understood by others. Therefore, communication research with individuals with LIS is unique in that the technologies being studied (e.g., BCI, functional MRI [fMRI], deep brain stimulation [DBS]) may become a tool for assessing or even restoring the capacity to give an informed consent.[15]

Ethical questions about ending BCI research participation in LIS have garnered less attention. BCI research in LIS involves both measuring brain activity and developing better algorithms for leveraging these measurements. As such, algorithmic utility is *discovered in the process of applying* those techniques to unique individuals. This feature of some BCI research— iterative customization of methods—makes negotiating study end-points in advance difficult, and makes post-hoc decisions about when to end research fraught. Participants (or surrogates) may not want to end their participation and researchers may continue to see value in collecting data and refining algorithms. Where (1) the goal of the research has not yet been achieved (i.e., establishing communication), (2) the participant and surrogate do not express a desire to withdraw consent for participation, and (3) the research continues to progress (to some extent) through incremental reduction in the design space, no natural stopping point may exist. This is potentially problematic, as research

with an indefinite horizon raises concerns about vulnerability and exploitation, just distribution of benefits and harms, coercion, and judicious use of research resources.

Researchers have ethical obligations to end BCI studies when participants no longer wish to continue or when studies cease to produce scientific value. But when neither of these are obviously the case, what are researcher obligations to end clinical studies? One approach to answering this question is to look at existing concepts or frameworks that ground researcher obligations to end randomized clinical trials (RCTs)—equipoise and nonexploitation—for guidance. Although equipoise and nonexploitation are useful for elucidating obligations to end RCTs, their applicability to exploratory BCI research is unclear. In this article, we present a recent actual case to illustrate the limitations of these frameworks. We conclude that an alternative framework based on fiduciary obligations is more promising. We sketch the outlines of this framework and offer a set of preliminary recommendations for BCI researchers. We hope to encourage further discussion of ethical problems arising from exploratory BCI studies.[16]

Case

Our group enrolled an individual with presumed LIS in a noninvasive BCI research study for the purpose of developing a reliable communication device. The research participant was a man in his 40s with a remote history of a brain stem stroke from a ruptured arteriovenous malformation resulting in the loss of all or nearly all voluntary movement.[17] In the 6 years following his stroke, he was observed at times to move his eyes horizontally, fixate on people and objects, and make subtle movements with his arm or foot to command, but these movements never allowed for a consistent means of communication. He was given a diagnosis of LIS. Attempts to find a reliable augmentative and alternative communication (AAC) method using eye movements (e.g., eye gaze) or voluntary muscle movement (e.g., switch) were unsuccessful.

With informed consent provided by his wife, the participant enrolled in a BCI study, followed by an iterative, user-centered design (UCD) study to create a binary choice or alphabetic communication system tailored to his functional abilities. Study visits took place at the participant's residence, an adult foster home. Visit scheduling accommodated the participant's health, the time required for system design and implementation, and the availability of the participant, his wife, and the researchers. The BCI study involved unsuccessful trials with a research-based P300 BCI system followed by a commercially available BCI system (which included P300 and motor imagery response paradigms). Classification accuracies with this system were not statistically different than chance. The UCD study involved collection of physiological data (electrooculogram [EOG], eye gaze, and/or electromyogram [EMG]) accompanied by visual and auditory cueing across multiple visits without a set timeline.[18] Flexible, repeated testing over an indefinite period was planned in order to customize the device for peak performance. The study had two aims: a formal scientific aim to contribute knowledge about new alternative access methods for individuals with minimal voluntary motor function, and a participant-specific aim to establish a new mode of communication. The research team proceeded under the assumption that the participant was capable of communicating, but lacked the physical means to do so consistently.

Over the course of 19 months, multiple modalities were employed in an attempt to establish a reliable brain signal for communication, but none were successfully validated. The study team visited the participant's home 14 times for a total of approximately 30 hours. The study team developed a system to aggregate repeated, error-prone trials into a single, accurate response selection.[19] The first modality attempted was an eyegaze-based interface given that the participant's strongest apparent input signal was his horizontal eye movement. A system using vertical bars of different colors moving horizontally across the screen as a means for binary yes/no communication (i.e., tracking a green bar indicating "yes" or red bar indicating "no") was constructed, but was ultimately unsuccessful. Drowsiness, fatigue, and ptosis confounded results, and attempts to mitigate these factors did not help. Successive use of alternative modalities (EOG and EMG) similarly failed to produce a validated system.

Our research team began to have doubts about the likely success of the project. The iterative protocol and the relationships developed between the team and the study participant and his wife (hereafter "participant pair") over the course of the study complicated a decision to end the study. The study had not produced a validated system. Although not all possible access methods and their respective customizations had been exhausted, the team expected diminishing returns from future iterations. Members of the team felt emotionally and morally conflicted about continuing the study. After much discussion, the participant's wife was consulted. She agreed that it was appropriate to end the current study because of the lack of promising results, but expressed a willingness to consider future research participation opportunities that might help her husband.

Equipoise and Ending BCI LIS Studies

Stopping rules for clinical trials are intended to protect human subjects from harm. Most often, stopping rules are employed in large RCTs in which the efficacy (or lack of efficacy) of an intervention becomes apparent before the completion of a study and in turn raises concern about harm to a study group (i.e., receiving a harmful intervention or missing out on a beneficial intervention). One rationale for stopping a clinical trial on the basis of efficacy is *equipoise*. Equipoise is an ethical construct used to justify initiating a research study. Put simply, a minimum ethical requirement for initiating a clinical trial is that a proposed intervention be in a state of equipoise, or uncertainty, as to efficacy. Were uncertainty not present, one study group would be subjected to an intervention known at the outset of the study to be inferior. This would be an unethical way to *start* a trial. Similarly, when data collected during a trial indicate that study groups are no longer in equipoise (e.g., one arm meets an efficacy end-point), it becomes unethical to *continue* a trial. In this section, we discuss some of the challenges of applying clinical equipoise to BCI LIS research.

The concept of equipoise was introduced by Charles Fried as a way to mediate conflicting obligations of clinician researchers: the physician's "fidelity" to the health of individual patients and the needs of the wider social group who stand to benefit from future therapies advanced through research.[20] The central idea is that when groups participating in clinical trials stand in equipoise relative to an intervention, neither group is knowingly sacrificed for the benefit of the other. Although a vigorous debate has ensued about how best to define

and operationalize equipoise,[21] equipoise has proved a resilient standard for design and evaluation of neuropharmacological,[22] neurosurgical,[23] and neurological device trials.[24]

Equipoise provides a framework for delineating ethical obligations of researchers to end studies. Efficacy findings from interim analyses bring to attention unanticipated or serious adverse effects or indicate the superiority of one trial arm to another. Researchers have ethical obligations to modify or stop a trial in light of the former and make a superior intervention available to all groups (or at least stop a trial and make a superior intervention known to all groups). Because equipoise has been employed to help resolve controversies associated with benefit–harm assessments and to provide a principled foundation for ending RCTs, equipoise also may provide ethical guidance for ending BCI LIS studies.

The application of equipoise to BCI LIS research faces challenges. One challenge is that the notion of equipoise relies on the existence of a standard of care against which an investigational intervention is compared, but currently individuals with presumed total LIS lack a standard best therapy for communication. There are forms of communication under investigation (e.g., fMRI or brain-implanted electrode arrays), although none have proven efficacious across diverse presentations of LIS.[25] As such, it can reasonably be argued that BCI research participants enrolled in a BCI research protocol do not forgo benefits of standard communication therapy by participating in research. Standard communication therapy is, unfortunately, *no* therapy.

A second challenge pertains to what Alex London calls the "fragile epistemic threshold" of equipoise.[26] If any new piece of data were sufficient to disturb equipoise, a mere hunch or a single positive or negative finding would tilt the balance away from equipoise in the minds of individual investigators, making it unlikely that any study would see completion. Therefore, critics of equipoise find its fragility a reason for abandonment as an ethical research framework.[27]

In the case of BCI LIS studies, establishing a robust threshold for equipoise is hindered by the size of the nascent field and its relatively underpowered studies. Systematic reviews and properly conducted RCTs represent the pinnacle of scientific evidence, whereas case reports, though a valuable contribution to a field's general fund of knowledge (particularly early in the development of a field) reside low on the evidence pyramid.[28] A robust threshold for equipoise requires that a research study *could* produce knowledge that would change expert opinion and consequently shift practice (i.e., establish a new standard of care). In the case of BCI LIS research, the likelihood of either at present is low. There is a legitimate worry that even if successful (i.e., development of a reliable communication algorithm for participant X) the results would be *unique to individual X* and insufficient to justify a change to clinical practice in general. As such, equipoise is unlikely to be as action guiding as we would want it to be.

Given these challenges, it is worth investigating an alternative to equipoise for understanding researcher obligations in BCI LIS research.

Nonexploitation and BCI LIS Studies

An alternative approach to researcher obligations in ending trials involves the concept of nonexploitation.[29] Ethically acceptable research involves risks to participants that are proportionate and reasonable relative to the knowledge gained

from the research. A trial should end if the benefits to science are no longer proportionate to the risks incurred by research participants. This can occur, for example, if the risks to participants increase during the course of a study or if the likelihood of generating scientific knowledge decreases.

Nonexploitation is difficult to operationalize when the benefits and harms experienced by research participants are opaque and difficult to assess. In BCI LIS studies, participants are unable to communicate whether participating has become more (or less) of a burden over time. Are BCI tasks (e.g., "find the letter R on the screen") experienced as a challenge that gives participants something enjoyable to pass the time or are they frustrating or boring? Are research activities a fun opportunity to interact with people—in a life that seems solitary—or do they take participants away from thinking about other things or even daydreaming? Is participating stigmatizing, a too-frequent reminder of what has been lost and of one's difference? Or is participating a way to have purpose, to be altruistic, or to contribute to the advancement of science? In the case of BCI LIS research, these questions cannot be fruitfully asked and answered directly of research participants, and although family can make surrogate assessments on behalf of participants, data on the divergence of quality of life assessments in ALS between patients and caregivers should at least give pause about substitute judgment.[30]

A framework of nonexploitation is also limited in cases in which the potential benefits to science emerge during the course of a study. An important feature of some BCI research is the iterative process of modifying interventions in response to participant feedback. Consider some examples. In a trial of BCI-controlled DBS for treatment of essential tremor, participants and researchers work together to modify volitional tasks in order to give participants control over turning on and off their implanted electrodes to suppress tremor.[31] Similarly, participants and research teams in the Braingate trial develop robotic prosthetics for individuals with paralysis through iterative processes of decoding motor intentions, giving better and better participant control over a robotic arm (e.g., to grasp objects).[32] And in the exploratory BCI LIS trial described here, the participant (presumably) and his wife work with the research team to try to establish a reliable neural signal (P300, EOG, EEG) by iteratively testing via communication-related tasks (e.g., intent to communicate mental content "I want the letter 's'"). The likely contribution to generalizable knowledge from BCI research projects like these—which incorporate iterative, open-ended methodology—may become much clearer well into the exploration. This complicates an appeal to nonexploitation insofar as it relies on an a priori grasp of the likely contribution to scientific knowledge.

Our review of equipoise and nonexploitation suggests that neither may be ideal tools for understanding the obligations of researchers to end BCI LIS research. It is worth asking why neither of these seem particularly promising for BCI LIS research. In the next section, we argue that there are three features of BCI LIS research that may underlie the difficulty of applying these approaches—multidisciplinary interdependence, participant collaboration, and therapeutic evolution—and that an approach that can better accommodate these features is preferred. We then suggest, following work by Miller and Weijer,[33] that understanding clinician-researcher obligations as fiduciary obligations is a preferred approach to accommodate these features.

Features of BCI Exploratory Research

Multidisciplinary Interdependence

BCI research is frequently conducted by multidisciplinary teams including engineers, computer scientists, neurologists, and allied health professionals such as speech-language pathologists, occupational and physical therapists, and others. Team members with technical expertise create new algorithms, interfaces, software, and hardware to improve BCI functionality, while those with clinical expertise bring familiarity with the needs, abilities, and opinions of potential BCI users. An important feature of BCI teams is integration of different types of expertise. Because devices are iteratively developed with research participants, those with technical and clinical expertise must work together in real time, rather than in parallel. Each iteration within a trial involves both new technical and clinical assessments. What are the chances that a change in algorithm or measurement technique will yield a desired outcome? What are reasonable possibilities? What are the potential harms to the participant in making this change? Will achieving a desired "technical" outcome improve the quality of life of the participant? The exploratory and iterative nature of BCI research demands a kind of back and forth between researchers possessing more technical or more clinical expertise. The result is a robust interdependence of expertise.

To illustrate this feature of multidisciplinary interdependence, consider the process of informed consent in the BCI LIS study described previously. Before initiation of the study, a process of informed consent was undertaken that involved not just clinicians, but engineers as well. Clinicians and engineers worked together to formulate "yes/no" questions that would accurately convey technical and clinical benefits and harms of participation. Engineers helped formulate questions describing the range of equipment and methods to be used as well as their likelihood of meeting statistical end-points, while clinicians translated these possibilities into meaningful outcomes for the participant, addressing their hopes, fears, and expectations. These questions were presented to the participant (and his wife) by both the clinicians and the engineers. Members of the team possessing both clinical and technical expertise were present to answer questions or provide clarifications, and to assess for affirmative or negative responses.[34]

Participant Collaboration

BCI research participants and caregivers are more than just subjects of research; in some instances they become collaborators of sorts. Exploratory BCI studies can extend for years, involve many time-intensive trial visits, and be highly individualized. Participants work *alongside* researchers toward a common goal (e.g., communication, control of a prosthetic amelioration of abnormal motor movements [e.g., tremor]), even to the point of participants feeling guilty when they put their needs ahead of project success (e.g., truncating a session because of fatigue).[35] Over the long course of a BCI study, participants and researchers become invested in each other, more than what might be accounted for by "anonymous user–researcher relationships."[36] Helen Mayberg describes a phenomenon in her long-term clinical studies of DBS for depression as people "starting as patients and ending up as collaborators" (personal communication). Participants (and surrogate decisionmakers) in BCI research do not always fit into traditional roles of participants,

volunteers, patients, or consumers, and instead may become more like collaborators or partners in research.

In the BCI LIS study described here, the participant's wife took on a collaborative role. At study initiation, she offered her intimate knowledge of the participant's physiological abilities and previous preferences in order to guide the design process. For example, she created and shared videos of the participant's eye and hand movements in response to command, allowing the team to better understand his abilities and limitations. In research team meetings, she highlighted challenges and offered potential solutions to problems of positioning, fatigue, and motivation, and contributed input to design choices (e.g., presenting vertical versus horizontal stimuli) and protocol implementation (e.g., conducting further iterations within a modality versus moving on to a new modality). She ensured that the participant was physically comfortable during visits and assisted with proper positioning of the equipment within his field of vision, suggesting modifications to improve performance. She also provided feedback on instructions and explanations provided to her husband by the researchers, requesting clarification and additional information for the participant and herself, when needed.

Therapeutic Evolution

Exploratory BCI trials generate therapeutic expectations. The notion that participants in research might *expect* therapeutic benefit is anathema to traditional research ethics, and the *therapeutic misconception*, as it has generally come to be known, is felt to undermine the validity of informed consent.[37] The therapeutic misconception has been identified in early stage pharmacological research[38] as well as neurological devices[39] and neurotechnology.[40] Although attracting comparatively less attention in BCI research,[41] the therapeutic misconception may be present as well. For example, Grübler found expectations of personal benefit among the motivations of participants in a BCI trial.[42] Although participants can enter BCI trials expecting therapeutic benefit, they can also *develop* therapeutic expectations over the course of trial involvement.

Iterations to methods in exploratory BCI trials are made in order to move participants toward some desired research goal (e.g., movement of a prosthetic, suppression of a tremor, or reliable response to verbal commands). If an algorithm fails to decode neural activity sufficient to detect a particular intention or allow control of a desired output, the algorithm is changed. In this way, exploratory BCI research embodies a kind of flexibility found more in clinical practice than in large research trials. Whereas the method (or methods) of measurement in a large pharmacological RCT, for example, is fixed and chosen in advance (e.g., the effect of drug X on outcome Y determined at time T), clinical interventions are flexible. A dose of a medication can be increased if it does not have the desired effect or decreased if it causes intolerable side effects. Clinical interventions are tweaked in order to get closer and closer to a desired clinical end (e.g., cancer remission, decreased bradykinesia, improved cardiac function). Similarly, iterations in exploratory BCI research, although formally directed at some research-delineated outcome— movement of a prosthetic, suppression of tremor, reliable response to verbal commands—come to be (or at least feel as if they are) oriented toward meaningful clinical ends: independent feeding of oneself (with a prosthetic), reduced stigma in public settings (with a suppressed tremor), or peace of mind (with effective communication

conveying one's needs). Therefore, even if therapeutic expectations were not present (or were even discouraged) at study start, they can develop over the course of a study.

Fiduciary Obligations in BCI Research

Miller and Weijer argue that the relationship between a clinician-researcher and a patient-subject is best understood as a *trust relationship*.[43] A trust relationship has three features. It involves structural inequality, it involves a transfer of discretionary power from the trusting party to the entrusted party, and it generates fiduciary obligations to protect and promote interests of the trusting party. The entrusted party (e.g., clinician-scientist) pursues goals that may at times conflict (e.g., produce generalizable knowledge versus improve a patient's immediate health status). When this happens, we should look toward fiduciary relationships as a model of obligations owed by clinician-researchers to research participants, including how to end research projects.

The researcher–participant relationships in BCI LIS research embody the three features of a trust relationship. First, the relationship between the research team and participant pair are certainly unequal in at least two respects. BCI interventions are primarily available only within research projects and, therefore, patients rely on the expertise of BCI teams to apply protocols in ways that could yield therapeutic benefit (e.g., the ability to communicate). In addition, BCI research teams possess specialized engineering knowledge that patients and surrogates do not possess, thus generating a kind of epistemic *inequality*.

Second, the participant pair grants *discretion* to the BCI team to oversee the participant's health interests, and in so doing, expose these interests to the risk of harm. The participant pair authorizes the team to collect confidential and sensitive information (e.g., about diagnosis, medical history, personality, and personal preferences), determine eligibility for participation in the project, design the study protocol (e.g., which modalities are included), and make adjustments during implementation of the iterative protocol (e.g., when to adjust settings or transition from one modality to another).

Third, because of the inequality between the BCI team and the participant pair and because of the considerable discretion afforded to the team across various dimensions of the study, the team incurs a *duty of care*. That is, team members are obligated to promote and protect the interests of the participant.

A framework of fiduciary obligation provides a way to approach questions of when and how to end BCI LIS research. The BCI team is entrusted to exercise some discretion over whether continued participation interferes with receiving competent and standard care for LIS and whether continued participation constitutes a failure to protect from undue harm. In the particular case discussed here, it was unknown whether continuing the study would generate harm. As previously discussed, there was uncertainty as to how much harm (if any) participation in the study caused. But in the absence of evidence from the participant about his subjective experience of research participation (e.g., inconvenience versus mental exhaustion versus enjoyment), the default fiduciary stance should be to presume that participation could cause *some* harm and that this should be taken seriously. The risk of harm is likely to vary considerably depending on the type of study, from minor inconvenience to physical discomfort, and should be considered on a

case-by-case basis. The role of a fiduciary is to keep possible harm always in mind so that when a study begins to show a decreasing likelihood of success, the study does not continue indefinitely but is brought to a reasonable end.

It should be noted that the idea that clinical researchers have fiduciary obligations to participants runs counter to a view of clinical research and medical practice as occupying morally distinct spheres. If medicine and research are, from an ethical standpoint, independent activities governed by different ethical principles, then fiduciary obligations that span the practices of medicine and clinical research do not make sense.[44] If so segregated, clinicians would seem to have their obligations and researchers would seem to have theirs.

A hard separation of research and practice has been challenged, not just by Miller and Weijer[45] but by others as well.[46] Various alternatives have been proposed, including applied patient-oriented research,[47] philosophy of clinical research,[48] and clinically oriented research.[49] Leaving aside the details of these views, all make room within clinical research for the pursuit of some therapeutic goals by researchers. A trust-based fiduciary framework can accommodate the kinds of therapeutic goals that result from BCI research that (1) is open-ended (like clinical care), (2) employs interventions iteratively adapted to achieve goals connected to the well-being of participants (such as clinical care), and (3) fosters ongoing trust relationships between researchers and participants (such as clinical care).

If there are therapeutic features of BCI LIS research that cannot be wholly separated from the pursuit of scientific goals, then there is an important shift that must take place in thinking about researcher obligations to end research. We must move away from chiding researchers and participants for "failing" to keep clinical and research apart in their goals, expectations, and decisionmaking. Instead, we should shift our efforts to helping navigate both the intersection and sometimes overlap of therapy and research. The pursuit of therapeutic goals can be an inherent part of motivation for and participation in research. Research teams have fiduciary obligations to manage therapeutic aspects of research through exercise of collective clinical judgment. One of these obligations pertains to ending research. Sketching what this fiduciary obligation looks like is the task to which we now turn.

Recommendations

We now offer some recommendations for how researchers can discharge their fiduciary obligations in exploratory clinical trials. These recommendations focus on multidisciplinary interdependence, participant collaboration, and therapeutic expectations of BCI research.

We recommend that multidisciplinary BCI teams understand their ethical obligations as primarily *shared responsibilities*. That is, individual team members may bring different forms of technical or clinical expertise to a research project, but ethical obligations attach to everyone by virtue of their membership on the team. A division of labor whereby "ethical issues" are the sole concerns of some members of the team (e.g., clinicians) and not of others, should be resisted. This does not deny that individuals bring different skills to the table (e.g., eliciting values, discussing fears, understanding device malfunctions), but these skills can be enhanced by how the team operates.

For example, deciding on the content of an informed consent discussion (including decision aids or consent forms) should be a team activity. Where possible, non-clinicians should be present for (even if not leading) informed consent discussions with potential participants, particularly if non-clinicians will have ongoing interactions with participants. Non-clinicians can clarify risks and possibilities of device performance that participants need in order to make informed decisions. This reduces the chance that one member of the team (e.g., clinician) will misunderstand or miscommunicate technical aspects of the study, but perhaps more importantly symbolizes that the *entire* team will look out for the participant's interests, even if one person is the designated study point of contact.

We recommend involving participants (and participant pairs) as *participant collaborators* in BCI research. Participants and participant pairs may desire, and different research protocols may allow, different types and levels of involvement (e.g., caregiver involvement in home device setup or maintenance). It is important to recognize that including participants as collaborators generates new responsibilities. Two are worth highlighting.

First, teams need to develop mechanisms for resolving conflicts and adjudicating differing expectations between participant collaborators and members of the BCI team. This should involve ongoing discussions throughout the study about roles and expectations, including feedback both from participants ("You should ask for my input more during the testing") and to participants ("Your suggestions on how to reduce participant fatigue were really useful"). Just as feedback to any member of a team needs to be given in a constructive and sensitive way, so too does feedback given to participant collaborators. Second, we recommend that elucidation and clarification of the desired role of participants become a formal part of a research project.[50] Participant collaborators may want to change their roles within the study as it progresses (e.g., a family member may want a reduced role if it becomes too burdensome or may want an enhanced role within the team because of a working understanding of the study and newfound comfort with the research environment).

We recommend that therapeutic expectations not be dismissed out of hand as a misconception but approached as an opportunity for *ongoing exploration* of participant values. Sometimes this exploration will involve tempering expectations of benefit where the likelihood of success is low, particularly at study outset (e.g., a low likelihood of developing a BCI speller versus a higher likelihood of identifying a promising yes/no communication scheme). That said, we recognize that different members of a research team—including participant collaborators—can hold different beliefs about the likelihood of benefit from trial participation (i.e., more realistic or less realistic). Within certain bounds, all of these beliefs can be rational. It is worth noting that therapeutic expectations may develop and change along the course of research participation, even if they were not present at study start and initial consent. For example, in a BCI study with positive communication outcomes for the participant, what happens when the study ends? The participant may be unable to obtain the system for independent home use, and will have experienced the ability to communicate only to have it taken away again. Therefore, it is sometimes more important to assess for therapeutic understanding and expectations in the *late* stages of a BCI project.

To facilitate meeting these fiduciary obligations in exploratory research, we recommend that BCI teams take the concrete step of formalizing "check-ins."

Ideally, the timing and content of these check-ins should be established at study outset and be well communicated to all members of the team, including participant collaborators (e.g., every 3 months). Assessments to take place during these check-ins should include: (1) interest of participants or participant pairs in continuing their participation, (2) emotional effects on participants and team members, (3) changing beliefs of team members about the likelihood of project success, and (4) changing roles or expectations of participants and team members. The primary purpose of these check-ins—made clear to all at study outset—is to provide the data needed for repeated discussions about the present and future of the project, including when it should end and under what conditions. Although participant collaborators should be encouraged to bring concerns or questions to the research team at any time, scheduled check-ins may ease the burden on participants and caregivers of initiating such conversations. Such a formalized process will not eliminate all ethical issues related to ending exploratory BCI trials, but may at least provide a tool for addressing some of them.

Notes

1. For definitions of LIS, see Bauer G, Gerstenbrand F, Rumpl E. Varieties of the locked-in syndrome. *Journal of Neurology* 1979;221(2):77–91 and Smith E, Delargy M. Locked-in syndrome. *Clinical Review British Medical Journal* 2005;330:406–9. The difficulty of distinguishing total LIS from a disorder of consciousness (e.g., persistent vegetative state [PVS]) based on a criterion of observable behavior has led some to offer the term "functional LIS" or "behaviorally unresponsive" patients who retain residual covert awareness. See Bruno MA, Vanhaudenhuyse A, Thibaut A, Moonen G, Laureys S. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. *Journal of Neurology* 2011; 258(7):1373–84 and Peterson A, Naci L, Weijer C, Cruse D, Fernández-Espejo D, Graham M, et al. Assessing decision-making capacity in the behaviorally nonresponsive patient with residual covert awareness. *AJOB Neuroscience* 2013;4(4):3–14. As will be noted in the case discussed here, we put this terminological debate to the side.
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16. We mean to distinguish exploratory research in a general sense from regulatory definitions of exploratory research, such as the United States Food And Drug Administration's (FDA) use of exploratory research to connote an investigational drug trial that "(1) is conducted early in phase 1; (2) involves very limited human exposure; and (3) has no therapeutic or diagnostic intent." See Guidance for industry, investigators, and reviewers on exploratory IND studies. FDA, January 2006; available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078933.pdf (last accessed 11 May 2018).
17. We have elected not to use the participant's real name because we are unable to obtain his consent for this. His wife, his surrogate decisionmaker, gave permission to discuss this case and their involvement in this research project.
18. We appreciate that for those who adopt a strict definition of BCI research—namely, that BCI research uses neural data exclusively—the current study may fail to meet this definition. EMG and EOG are often equally encouraging directions of research. EMG measures muscle activity via electrodes placed on the surface of the skin, whereas EOG is a special type of EMG that relates to eye movement. In this article, we take the more inclusive view that a BCI study can include both neural data and non-neural data (EOG, EMG, eye gaze).
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34. Questions were read aloud to the participant (and repeated several times), but the researchers did not elicit reliable verbal or motor responses. The participant's wife felt that he *did* respond affirmatively to some of these questions through eye movements, but researchers were unable to confirm these. The participant's wife provided surrogate consent for research participation.
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50. Clarification of roles may require concomitant development of new terminology to label these roles. For example, the terms "team" and "team members" are ambiguous as to whether participants and caregivers are encompassed by these terms. Additional terminology may need to be adopted (e.g., the "researcher team," which is subject to regulatory oversight versus the broader "project team," which also includes research participants and caregivers). To avoid confusion in describing the current study, we have kept, somewhat reluctantly, to the convention of using "team" to only refer to traditional researchers (not the participant and family), in the case described here, a speech-language pathologist and two engineers.